

REMARKS

Applicants filed Amendment C and a RCE on November 21, 2003 in response to the Final Rejection of July 22, 2003 and the subsequent Advisory Action of October 31, 2003. Applicants have the following response to the Office Action of February 18, 2004.

Claim Amendments – Reference to Disclosure

Independent Claims 1 and 19 have been amended to bring them into better conformance with the disclosure in the specification. In particular, these claims are now more explicitly directed to intracorporeal pharmaceutical compositions consisting of aqueous solutions, tablets, capsules, suppositories or syrups. Examples in support of such claimed pharmaceutical compositions are found, for instance, in paragraph 5 of the specification as follows:

“[0005] ... medicaments are suitable for *intracorporeal administration*, and are thus intracorporeal chemotherapeutic medicaments.... such medicaments can also be called *pharmaceutical compositions* or agents.” (emphasis added)

Accordingly, this passage supports that medicaments, as previously recited in independent Claims 1 and 19, may alternatively be described as pharmaceutical compositions. Such nomenclature has been applied to amended independent Claims 1 and 19, as well as to those claims dependent thereupon, as Applicants believe that such claim language is a more accurate description of the claimed invention. Applicants respectfully submit that such amendments have not added new subject matter nor narrowed the scope of such claims.

Similarly, examples in support of the amendment to recite aqueous solutions in independent Claims 1 and 19 are found, for instance, in paragraphs 34-38 of the specification as follows:

“[0034] ...A solution of Rose Bengal (50-100 µL of 0.5% Rose Bengal in saline) was ... administered by intraperitoneal injection (i.p.) to ... tumor-bearing mice, and the injected mice sacrificed at timed intervals following injection.... The data in FIGURE 2 show that Rose Bengal rapidly diffuses from normal tissue ... [whereas] persistent accumulation occurs in tumor tissue, with greater than 50% of maximum measured agent concentration maintained in such tissues for periods in excess of 24 hours.

“[0035] If such implanted tumors are directly injected with Rose Bengal, similar selective, persistent accumulation occurs.

“[0036] For example, BNL/SV40 liver cell [tumors injected with] a 10% solution of Rose Bengal (50 µL of 10% Rose Bengal in saline) resulted in marked red staining of the tumor and the surrounding flank. Within 7 days this Rose Bengal cleared from normal tissue, but the tumor tissue remained stained. Over a period of several weeks the previously rapidly growing tumor exhibited stasis....

“[0037] Further, peritumoral injection alone (e.g., injection into normal tissue around the outside margins of the tumor) of the above Rose Bengal exhibited no detectable retention in normal tissue after 24 hours.

“[0038] Hence, the administered Rose Bengal in these examples not only exhibited selective, persistent accumulation in tumor tissue, but this accumulated agent also exhibits chemotherapeutic efficacy with minimal or no measurable side effects in healthy tissue.”

This passage supports that the pharmaceutical compositions of independent Claims 1 and 19, may consist of aqueous solutions of a halogenated xanthene, such as rose bengal. Amended independent Claims 1 and 19, as well as to those claims dependent thereupon, now reflect such disclosure. Hence, Applicants respectfully submit that such amendments have not added new subject matter.

Similarly, examples in support of the amendment to independent Claim 19 to recite tablets, capsules, suppositories or syrups are found, for instance, in paragraphs 24 and 49 of the specification as follows:

“[0024] In a preferred embodiment, such medicaments are produced in various formulations suitable for intracorporeal or topical administration, including in various liquid, semisolid, solid or aerosol delivery vehicles, as well as in *tablet*, *capsule*, *suppository*, and other similar forms.” (emphasis added)

“[0049] It is thus a further preferred embodiment of the present invention that at least one halogenated xanthene or halogenated xanthene derivative be formulated as a medicament in a form suitable for intracorporeal or topical administration ... [including] aqueous, non-aqueous or particulate suspensions, solutions, creams, ointments, gels, *syrups*, micro-droplet sprays, *suppositories*, *tablets* and *capsules*.[”]
(emphasis added)

These passages illustrate that the pharmaceutical compositions of independent Claim 19 may consist of tablets, capsules, suppositories or syrups containing a halogenated xanthene, such as rose bengal. Amended independent Claim 19, as well as those claims dependent thereupon, now reflect such disclosure. Hence, Applicants respectfully submit that such amendments have not added new subject matter.

Examples in support of the amendment to Claims 1 and 19 to recite sodium or potassium salt of a halogenated xanthene are found, for instance, in Table 1 of the present application, which illustrates that groups R¹ and/or R² of the halogenated xanthenes (see Figure 1a for the structural designation of these groups) may be, for example, sodium (Na) or potassium (K). This particular identity of the claimed halogenated xanthenes is further illustrated by Figure 1b, which shows rose bengal in its dibasic form (i.e., as a disodium salt). Hence, Applicants respectfully submit that such amendments have not added new subject matter.

Accordingly, for at least the above-stated reasons, it is respectfully submitted that the amendments to the claims are clearly supported by the application as filed. Therefore, it is requested that they be entered.

Finally, in order to advance the prosecution of this application Applicants have canceled Claims 5-8, 23-26, 31 and 33.

Applicants will now address each of the Examiner's comments and rejections in the order in which they appear in the Office Action.

Response to Amendment

In the Office Action, the Examiner notes that, on page 7 of Applicant's response of November 21, 2003, Applicants inadvertently stated that "Claims 28-20" were canceled. The Examiner is correct that the Applicants intended to state that Claims 28-30 were canceled.

Claim Rejections – 35 USC §102

Rejection over Williams

The Examiner also rejects Claims 1-4, 7-8, 10-11, 19-22, 25-27, 31 and 33 under 35 U.S.C. 102(b) as being anticipated by Williams et al. This rejection is respectfully traversed for at least the following reasons. As explained in more depth below, Williams does not disclose or suggest the claims, as presently amended, for at least several reasons.

First, Williams does not describe the claimed injectable solution, but rather is limited to topical gels, lotions, creams and ointments. This is made clear in Williams' detailed description of the invention, such as for example in the following:

"Vascular tissue of neoplastic and neovascular lesions as well as abnormal collections of vascular tissue are sensitized to light by the *topical application* of a light sensitizing agent. When later exposed to laser energy of a level sufficient to induce intravascular coagulation, i.e., a blood clot inside the vessel blocking blood flow through the vessel, rather than burn or destroy the tissues." [col. 3, lines 46-52, emphasis added]

"*Photosensitizing agents* that can be used are those that will render blood in target tissues sensitive to coagulation from exposure to light. Exemplary agents and

a few of the light frequencies to which they are sensitive *include ... rose bengal* (550 nm)....” [col. 5, lines 7-14, emphasis added]

“Unformulated *photosensitizing agents cannot be applied topically and be effective* for photodynamic therapy. The agents would not adhere properly, would immediately diffuse away from the target tissues, ... and would not be readily applied. Storage and delivery formulations are used to overcome such problems. Suitable formulations will be in combination with *penetrating solvents* or be in the form of a *gel, lotion, cream, or ointment....*” [col. 5, lines 42-51, emphasis added]

*The photosensitizing agents may be formulated for *topical* application in *penetrating solvents* or in the form of a *lotion, cream, ointment or gel.* . . . “[col. 5, lines 54-56, emphasis added]

Thus, Williams teaches that the disclosed *photosensitizing agents*, such as rose bengal, *must be formulated with a penetrating solvent or in a gel, lotion, cream or ointment* to facilitate topical administration. To this end, Williams lists a large number of penetrating solvents for enhancing penetration into tissue:

“Suitable penetrating solvents are solvents ... which will enhance percutaneous penetration of the [photosensitizing] compound. Solvents which have this property include proparacaine, dimethyl sulfoxide,” [see col. 6, line 56 - col. 7, line 6]

Accordingly, Williams teaches away from an intracorporeal pharmaceutical compositions consisting of an aqueous solution, as recited in the claims of the present application, since such aqueous solutions do not incorporate Williams' penetrating solvents.

Second, in addition to an aqueous solution, Williams teaches away from intracorporeal pharmaceutical compositions in delivery vehicles consisting of tablets, capsules, suppositories or syrups, as recited in the claims of the present application. Instead, as described supra, Williams teaches that photosensitizers, in order to be effective, must be formulated in a “gel, lotion, cream,

or ointment" for topical delivery (see e.g. Williams, col. 5, lines 42-51). This position is reinforced by all the examples provided in Williams as demonstrated below:

"Example 1

"A formulation effective for photodynamic therapy according to the invention is prepared with the materials listed in table 1.

"TABLE 1

Ingredient	Concentration
DHP (photosensitizing agent)	75 mg
EDTA (preservative)	30 mg
carboxymethylcellulose (viscosity agent)	600 mg
isotonic saline (diluent)	30 ml

"The photosensitizing gel formulation is made by adding the carboxymethylcellulose polymer to 10.5 ml saline.... This mixture is stirred until a gel is formed.... The porphyrin and EDTA are dissolved in sterile saline... Under aseptic conditions, the porphyrin/EDTA solution is added to the gel.... [col. 8, lines 3-26]

"Example 2

"The gel of example 1 was topically applied... to New Zealand rabbits in which CNV had been induced.... The amount of DHP penetrating through the epithelium into the cornea was markedly increased by pretreatment with proparacaine application of the DHP gel.... [col8, lines 29-44]

"Example 3

"The photosensitizing gel formulation of example 1 was used topically in the treatment of corneal vascularization of six human patients...." [col. 8, lines 46-56]

Thus, the gel described in all of the examples in Williams is a topical preparation and is clearly not an intracorporeal pharmaceutical composition in a delivery vehicle consisting of a tablet, capsule, suppository or syrup, as recited in the claims of the present application.

For at least the aforementioned reasons, Williams not only fails to teach or suggest the presently claimed intracorporeal pharmaceutical compositions, consisting of aqueous solutions, tablets, capsules, suppositories or syrups, but in fact, Williams *teaches away* from such formulations by requiring compositions formulated “with a penetrating solvent or in a gel, lotion, cream or ointment.” Accordingly, Claims 1-4, 7-8, 10-11, 19-22, 25-27, 31 and 33 are not disclosed or suggested by Williams and are patentable there over. Therefore, it is respectfully requested that this rejection be withdrawn.

Rejection over Goers

The Examiner also continues to reject Claims 1, 3-8, 19, 21-26 and 31-33 under 35 U.S.C. 102(b) as being anticipated by Goers et al. This rejection is also respectfully traversed. For at least the reasons discussed below, Goers does not disclose or suggest the amended claims.

First, as explained in depth in Amendments B and C, Goers does not describe the presently claimed chemotherapeutic pharmaceutical compositions, since commerce in such compositions in the U.S. would require specific labeling of such compositions regarding, among other features, indication and usage. Such labeling (i.e., chemotherapeutic compositions according to the claims of the present application) would readily distinguish any such patented product from any product based on the teachings in Goers. For example, for the invention of Goers to be practiced as a pharmaceutical composition, it would require labeling for indication (i.e., as a photosensitizer) and use (i.e., apply product, then apply a specific wavelength and amount of light to cause product to work) that clearly distinguishes it from the claimed compositions (i.e., chemotherapeutic compositions where one just administers the product; unlike a photosensitizer, the product does not

require additional light application in order to function). No user of such products would confuse the photosensitizer product of Goers and the chemotherapeutic product of the present application.

Second, Goers requires conjugate agents that are chemically distinct from those claimed in the present application. Goers is unambiguous on this fact. For example, Goers states:

“In vivo administration may involve use of therapeutic agents *of antibody therapeutic agent conjugates* in any suitable adjuvant including serum or physiological saline, with or without another protein, such as human serum albumin.”
(col. 28, lines 33-37, emphasis added)

Further, any alleged superficial similarity between the disclosure in Goers and the claims of the present application is eliminated by the amendments herein to independent Claims 1 and 19, with both claims being directed to sodium or potassium salts of the halogenated xanthenes. Such salts are not antibody conjugates, and are different than the compounds disclosed in Goers. In fact, the teachings of the present application demonstrate that the conjugates of Goers represent an unnecessary complication and the claimed invention *excludes* such conjugate agents. Thus, Goers teaches away from the claimed invention and a fundamental aspect of the present application, namely that the halogenated xanthenes exhibit remarkable pharmacologic properties without requirement of exotic delivery formulations (such as liposomes) or antigenic conjugates (such as antibody-agent conjugates).

For at least the above-stated reasons, Goers not only fails to teach or suggest the presently claimed chemotherapeutic pharmaceutical compositions, consisting of sodium or potassium salts of the halogenated xanthenes, but Goers actually teaches away from such compositions by requiring compositions comprising “antibody therapeutic agent conjugates.” Accordingly, the claims are

patentable over the cited reference, and it is respectfully requested that this rejection of Claims 1, 3-8, 19, 21-26 and 31-33 under USC 102(b) over Goers be withdrawn.

Rejection over Bottiroli

The Examiner also continues to reject Claims 1-11, 19-27 and 31-33 under 35 U.S.C. 102(b) as being anticipated by Bottiroli et al. This rejection is also respectfully traversed, as Bottiroli does not disclose or suggest the amended claims.

First, as explained in depth in Amendments B and C, Bottiroli does not describe the presently claimed chemotherapeutic pharmaceutical compositions, since commerce in such compositions in the U.S. requires specific labeling regarding, among other features, indication and usage. As described supra with reference to Goers, the photosensitizers in Bottiroli are readily distinguishable from any product based on the teachings of the present application. No user of such products would confuse the photosensitizer product in Bottiroli with any chemotherapeutic product of the present application.

Second, Bottiroli requires conjugate agents that are chemically distinct and different from the claimed compositions of the present application. Bottiroli is unambiguous on this fact, for example, as illustrated by the following passage:

“Fluorogenic substrates in the present invention are *derivates* of xanthenes ... containing quencher groups....” (p. 3, lines 22-24, emphasis added)

Thus, Bottiroli teaches that for any xanthene to have use in a pharmaceutical composition, it must be a specific derivative containing special fluorescence quencher groups. That Bottiroli teaches

away from any non-derivative form of the xanthenes (such as the sodium or potassium salts of amended Claims 1 and 19 of the present application) and the claimed invention is demonstrated by the structures of rose bengal and rose bengal acetate (shown on p. 4 of the reference), which Bottiroli identifies as clearly distinct compounds (rose bengal acetate is an example of a xanthene derivative taught by Bottiroli).

Moreover, as described in Amendment B, Bottiroli also fails to demonstrate or suggest utility of the non-derivative forms of the xanthenes (as evidenced, for example, by Bottiroli's cellular vitality data on p. 7, lines 16-20). This ill-conceived experiment is presented in Bottiroli as prima facie evidence that non-derivative forms of xanthenes are not therapeutically useful (i.e., not useful in pharmaceutical compositions).

Hence, the disclosure in Bottiroli and the amended claims of the present application, which are directed to sodium or potassium salts of the halogenated xanthenes, are clearly different and distinct. The claimed salts are not xanthene derivatives containing quencher groups as required in Bottiroli. Moreover, the teachings of the present application demonstrate that such derivatives in Bottiroli represent an unnecessary complication. Thus, as noted supra with reference to the cellular vitality data presented by Bottiroli on p. 7, Bottiroli goes to considerable length to teach away from the claimed invention and a fundamental aspect of the present application, namely that the halogenated xanthenes exhibit remarkable pharmacologic properties without requirement of exotic delivery formulations (such as liposomes) or special conjugates (such as quencher-agent conjugates).

For at least the above-stated reasons, Bottiroli not only fails to teach or suggest the presently claimed chemotherapeutic pharmaceutical compositions, consisting of sodium or potassium salts of the halogenated xanthenes, but Bottiroli teaches away from such compositions by requiring

compositions comprising “derivates of xanthenes ... containing quencher groups.” Accordingly, the claims are patentable over this reference, and it is respectfully requested that the Examiner’s rejection of Claims 1-11, 19-27 and 31-33 under USC 102(b) over Bottiroli be withdrawn.

Rejection over Schultz

The Examiner also continues to reject claims 1, 3-6, 19, 21-24 and 31-33 for alleged anticipation by Schultz et al. This rejection is also respectfully traversed as Schultz does not disclose or suggest the claims, as presently amended, for at least the following reasons.

First, similar to that discussed supra with respect to Goers and Bottiroli, Schultz requires the use of conjugate agents, as illustrated by the abstract therein:

“*Polypeptide compositions* are provided having a binding site specific for a particular target ligand and further *having an active functionality* proximate the binding site. The *active functionality may be a reporter molecule* Alternatively, the *active functionality may be a chemotherapeutic agent*, in which case the polypeptide compositions are useful for therapeutic treatment of various diseased states.” (emphasis added)

Thus, the compositions in Schultz are conjugate compositions (containing either diagnostic or therapeutic agents, depending upon the type of “active functionality” attached to the polypeptide). In contrast, as described supra for the rejection over Goers and Bottiroli, amended independent Claims 1 and 19 of the present application, *exclude* such conjugate agents. Specifically, each independent claim clearly delineates that the sole active component consists of a sodium or potassium salt of a halogenated xanthene. Such salts are not conjugates of halogenated xanthenes. Accordingly, the agents in Schultz are not encompassed within the independent claims of the present application. Since the invention of the independent claims is free of the limitations required in

Schultz and different than what is disclosed in Schultz, Schultz does not disclose or suggest, and cannot anticipate nor render obvious, the claimed invention.

Second, Schultz does not teach or suggest a therapeutic use of rose bengal or any halogenated xanthene. Instead, Schultz describes two separate categories of conjugated polypeptides, namely (a) diagnostic conjugate agents and (b) therapeutic conjugate agents. For example, Schultz states:

“Novel polypeptides having binding sites capable of specifically binding a predetermined target ligand include at least one active functionality proximate the binding site.... *The active functionality may be a reporter molecule*, whereby the polypeptides will be *useful in detecting* the predetermined target ligand in a sample suspected of containing such ligand.... *Alternatively, the active functionality may be a chemotherapeutic agent*, whereby the polypeptide will be *useful in treating a diseased state* by site-specific drug delivery.” (col. 4, line 58 - col. 5, line 6, emphasis added)

Thus, the reporter-molecule conjugate in Schultz is for *diagnostics* (i.e., “detecting the predetermined target ligand in a sample”) while the chemotherapeutic-molecule conjugate is for *treatment*.

The respective identities of the two distinct classes are established by several passages therein, including the following:

“*Reporter molecules* and compounds are selected to provide a detectable signal *Suitable reporter molecules include* chromogens (e.g., dyes and fluorophores)....

“A wide variety of fluorescers may be employed either by themselves or in conjunction with quencher molecules. *Fluorescers of interest* fall into a variety of categories having certain primary functionalities. These primary functionalities *include ... xanthene....*

“*Individual fluorescent compounds* which have functionalities for linking or which can be modified to incorporate such functionalities *include ... rose bengal....*” (col. 9, line 32 - col. 10, line 27, emphasis added in Schultz)

In this passage, Schultz teaches that the xanthenes comprise one of several classes of “fluorescers of interest,” and rose bengal is listed as a specific *fluorescent compound* of interest. Thus, Schulz teaches that xanthenes, and in particular rose bengal, are for *diagnostics* (i.e., as fluorescent diagnostic reporter molecules when conjugated to certain polypeptides).

Schultz describes a separate class of chemotherapeutic agents, and teaches the following:

“Chemotherapeutic agents will be selected depending on the diseased state which is being treated as well as on the nature of the target ligand.... Exemplary chemotherapeutic agents include toxins, toxin fragments, bactericides, radical scavengers, radical generators, alkylating agents, neurotransmitters, radionuclides, antiviral compounds, antifungal compounds, antineoplastic agents, antimycoplasmal agents, heavy metals, and the like. A list of suitable drugs is provided in Table 1. (col. 11, lines 8-21)

In contrast to the abovementioned case for “reporter molecules,” Schultz fails to include xanthenes or rose bengal in this list of chemotherapeutic agents (this is also the case for Table 1 in the reference). Accordingly, despite reference to for rose bengal for diagnostics, Schultz fails to disclose or suggest any therapeutic or chemotherapeutic role for rose bengal or any other halogenated xanthene and therefore fails to disclose or suggest the claimed chemotherapeutic pharmaceutical compositions of the present application.

Thus, for at least the above-stated reasons, Schultz not only fails to teach or suggest the presently claimed chemotherapeutic pharmaceutical compositions, consisting of sodium or potassium salts of the halogenated xanthenes, but Schultz also teaches away from such compositions by requiring conjugates attached to “novel polypeptides.” Accordingly, the claims are patentable thereover, and it is respectfully requested that the Examiner’s rejection of Claims 1, 3-6, 19, 21-24 and 31-33 under USC 102(b) over Schultz be withdrawn.

For at least the above-stated reasons, it is respectfully submitted that each of the §102 rejections has been overcome, and it is requested that they be withdrawn.

Claim Rejections – 35 USC §103

Finally, the Examiner continues to reject Claims 2 and 20 under 35 U.S.C. 103(a) as being obvious over Goers et al. This rejection is also respectfully traversed, for at least the following reasons, as Goers fails to disclose or suggest the claimed invention.

First, Goers requires conjugate agents; the claimed invention does not. As discussed supra with respect to the Examiner's allegation of anticipation by Goers, Goers requires the use of conjugate agents. In contrast, the claimed invention, as herein amended, *excludes* such conjugate agents. Further, Goers teaches that, to produce a functioning pharmaceutical composition, such *conjugate agents are necessary*. In contrast, the present application teaches that such *conjugates are unnecessary*. For at least this reason, the teachings in Goers do not render the claimed invention obvious.

Second, Goers requires photosensitization; the claimed invention does not. Also as discussed supra with respect to the Examiner's allegation of anticipation by Goers, Goers requires the use of photoactivation with its conjugate agents. In contrast, the claimed invention does not require such photoactivation. Furthermore, Goers teaches that, to produce a functioning pharmaceutical composition, such *photoactivation is necessary*. In contrast, the present application teaches that such *photoactivation is unnecessary*. The present application teaches halogenated xanthenes that yield a highly desirable pharmacologic outcome (i.e., treatment of cancer, etc.) and

that do not require the complexities of photoactivation (i.e., uniform delivery of activating light to a treatment region).

In addition, for treatment of for example, a brain tumor, the claimed application is not only superior (in that light doesn't have to be delivered somehow into the head) to that taught in Goers but Goers predicts that such chemotherapeutic treatment could not work. Hence, the teachings in Goers do not render the claimed invention obvious over Goers.

Since the therapeutic agents of the claimed invention entail neither (a) conjugation to any targeting moiety in order to function properly, nor (b) activation using light energy applied after delivery to their target tissue, and since both such features are required by Goers, the teachings in Goers are contrary to those of the claimed invention and cannot, therefore make the claimed invention in part or as a whole obvious.

Therefore, for at least the reasons discussed above, it is respectfully requested that the §103 rejection be withdrawn.

Interview Request

If the Examiner still wishes to reject the claims of the present application after considering this amendment, then Applicants request an interview with the Examiner to discuss the rejections in further depth. Please contact the undersigned to set-up such an interview.

Conclusion

For at least the above-stated reasons, it is respectfully submitted that the claims of the present application are in an allowable form and are patentable over the cited references. Accordingly, it is requested that the application now be allowed.

If any fee should be due for this amendment, please charge our deposit account 50/1039.

Favorable reconsideration is earnestly solicited.

Respectfully submitted,

Date: August 17, 2004



Mark J. Murphy
Registration No. 34,225

COOK, ALEX, McFARRON, MANZO,
CUMMINGS & MEHLER, Ltd.
200 West Adams Street, Suite 2850
Chicago, Illinois 60606
(312) 236-8500